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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/762,888

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Anthony J.F. d'Apice

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EXAMINER

CHEN, SHIN LIN

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/762,888

Applicant(s)

D'APICE ET AL.

Examiner

Shin-Lin Chen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 May 2006.
2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
4a) Of the above claim(s) 11 and 12 is/are withdrawn from consideration.
5) ☒ Claim(s) 6-10 is/are ~~allowed~~ allowable.
6) ☒ Claim(s) 1-5 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 21 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 1-21-04 & 2-2-06.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of group I, claims 1-10, in the reply filed on 5-8-06 is acknowledged.

2. Claims 11 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election was made **without** traverse in the reply filed on 5-8-06.

Claims 1-12 are pending and claims 1-10 are under consideration.

Priority

3. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), **the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.**

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months

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from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

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The preliminary amendment filed 1-21-04 regarding the specification fails to specify the relationship of the applications claimed with priority.

Specification

This application contains sequence disclosures that are encompassed by the definition for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there is no sequence identifier for the nucleotide sequence in Figures 4, 5, 16, 26 and 27 or in the "BRIEF DESCRIPTION OF THE DRAWINGS". Each nucleotide sequence is required to have a sequence identifier. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 1 recites the limitation "the DNA construct" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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7. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for generating a porcine cell comprising at least one inactivated alpha-1,3 galactosyltransferase gene in vitro, does not reasonably provide enablement for a method for generating a porcine cell comprising at least one inactivated alpha-1,3 galactosyltransferase gene in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-5 are directed to a method for generating a porcine cell comprising at least one inactivated alpha-1,3 galactosyltransferase gene by introducing into said cells a DNA construct comprising a disrupted porcine alpha-1,3 galactosyltransferase gene, wherein the disruption is by insertion of an exogenous sequence, such as a selectable marker, and the gene encodes a porcine alpha-1,3 galactosyltransferase with an amino acid sequence of SEQ ID No. 10 before the disruption. Claim 2 specifies the disruption is within exon 4, 7, 8, or 9. Claim 4 specifies the selectable marker is either neo^R gene or the nyg^R gene. Claim 5 specifies the exogenous sequence is flanked by FRT DNA elements and stop codon has been inserted 3' to the selectable marker for each of the three reading frames for the porcine alpha-1,3 galactosyltransferase gene.

The claims encompass generating a porcine cell comprising at least one inactivated alpha-1,3 galactosyltransferase gene by introducing into said cells a DNA construct comprising a disrupted porcine alpha-1,3 galactosyltransferase gene in vivo. There must be a purpose in generating a porcine cell comprising at least one inactivated alpha-1,3 galactosyltransferase gene in vivo. The specification states that "[t]his invention relates generally to the field of xenotransplantation. In particular this invention relates to methods and materials for reduction or

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elimination of the hyperacute rejection response in humans. More particularly, this invention relates to methods for treating human serum to reduce or eliminate hyperacute rejection” (see specification, p. 1, lines 9-15). Therefore, the claims read on gene therapy *in vivo* for reduction or elimination of the hyperacute rejection response in humans.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Verma et al., Sept. 1997 (Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma states that “The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses.” (e.g. p. 239, column 3). The adenoviral vector can induce both cell-killing “cellular” immune response and the antibody-producing “humoral” immune response from the host. The virally infected cells can be killed by cytotoxic T lymphocytes and the humoral response results in the generation of antibodies against adenoviral proteins. “There are considerable immunological problems to be

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overcome before adenoviral vectors can be used to deliver genes and produce sustained expression” (e.g. p. 241, left and middle column).

Eck et al., 1996 (Goodman & Gilman’s The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein’s compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that “the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression” for gene therapy, and obstacles to gene therapy *in vivo* include “the development of effective clinical products” and “the low levels and stability of expression and immune responses to vectors and/or gene products” (e.g. abstract). Thus, administration route plays an important role in gene transfer efficiency.

The specification fails to provide adequate guidance and evidence for how to generate a porcine cell comprising at least one inactivated alpha-1,3 galactosyltransferase gene *in vivo* by introducing a DNA construct into said cell so as to reduce or eliminate hyperacute rejection in a human subject. As discussed above, poor gene transfer efficiency is a big problem in gene delivery *in vivo*, host immune response to the adenoviral vector and administration route all play important role in gene transfer efficiency. The specification fails to provide adequate guidance

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for how to generate porcine cells comprising at least one inactivated alpha-1,3 galactosyltransferase gene in vivo by using various vectors via various administration routes, such as oral administration, intraperitoneal injection, topical administration, intravenous administration, intramuscular injection, and subcutaneous administration etc., in vivo such that the produced porcine cells could be used to reduce or eliminate hyperacute rejection in a human subject. There is no evidence of record that shows administration of a vector, such as adenoviral vector, comprising a disrupted porcine alpha-1,3 galactosyltransferase gene into porcine cells in vivo via various administration routes can produce porcine cells that could be used to reduce or eliminate hyperacute rejection in humans. The specification also fails to provide adequate guidance for how to use the claimed porcine cells to reduce or eliminate hyperacute rejection in a human subject. Absent specific guidance, one skilled in the art at the time of the invention would not know how to generate porcine cells comprising at least one inactivated alpha-1,3 galactosyltransferase gene in vivo by using various vectors via various administration routes such that the produced porcine cells could be used to reduce or eliminate hyperacute rejection in a human subject.

In view of the unpredictable nature of gene therapy and gene transfer in vivo, the host immune response to certain vector, and the lack of specific guidance, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

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Conclusion

Claims 1-5 are rejected. Claims 6-10 are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.



**SHIN-LIN CHEN
PRIMARY EXAMINER**